



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP00/02345 (22) International Filing Date: 16 March 2000 (16.03.00) (30) Priority Data: MI99A000625 26 March 1999 (26.03.99) IT (71) Applicants (for all designated States except US): BIOINDUSTRIA LABORATORIO ITALIANO MEDICINALI S.P.A. [IT/IT]; Via De Ambrosiis, 2-4-6, I-15067 Novi Ligure (IT). CARACCIA, Nicola [IT/IT]; Via De Ambrosiis, 2-4-6, I-15067 Novi Ligure (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): TENCONI, Franco [IT/IT]; Via De Ambrosiis, 2-4-6, I-15067 Novi Ligure (IT). GIORDANI, Cristiana [IT/IT]; Via De Ambrosiis, 2-4-6, I-15067 Novi Ligure (IT). (74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: A PROCESS FOR THE PREPARATION OF GABAPENTIN		
(57) Abstract A process for the preparation of gabapentin starting from gabapentin hydrochloride, which comprises the following steps: preparing a gabapentin hydrochloride aqueous solution; adjusting the pH of said solution to or about to gabapentin isoelectric point by addition of a basic compound comprising a monovalent anion; diafiltering said solution through a membrane highly selective for organic compounds with molecular weight higher than 150 and poorly selective for inorganic monovalent ions, to separate said solution into an aqueous permeate containing chloride ions and a retentate containing unsalified gabapentin substantially free from chloride ions; concentrating said retentate by increasing the pressure exerted on said membrane to obtain a concentration of unsalified gabapentin in the retentate not lower than 5 %; evaporating the retentate under reduced pressure and at T° < 35°; precipitating gabapentin by addition of an alcohol.		

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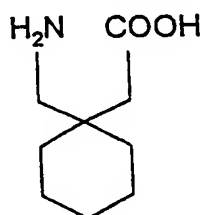
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A PROCESS FOR THE PREPARATION OF GABAPENTIN

The present invention generally relates to the pharmaceutical chemistry field.

5 More particularly, the invention relates to process for the preparation of 1-(aminomethyl)-1-cyclohexanecarboxylic acid, also known under the name gabapentin, having the following chemical structure:



Gabapentin is an active ingredient used in the treatment of various cerebral diseases, such as epilepsy, hypokinesia, cranial traumas and the like and is the object of US 4 024 175 and US 4 087 544.

20 A number of processes for preparation of gabapentin are reported in literature; US 4 024 175, for example, discloses some preparation methods starting from cyclohexyl-1,1-diacetic acid.

25 All the prior art processes yield, however, gabapentin hydrochloride, which has then to be transformed into the free amino acid by treatment with a basic ion exchanger followed by crystallization from an ethanol/ether mixture.

30 US 4 894 476 discloses a process for the transformation of gabapentin hydrochloride into the free amino acid, which comprises passing an hydrochloride aqueous solution on a ion exchange resin column with use of large water volumes.

Due to the high water solubility of unsalified gabapentin, large water volumes have to be evaporated off

in order to recover said compound, operating at low temperatures to prevent the formation of lactams. This makes said process hardly convenient from the industrial point of view.

5 Alternative methods have been suggested to overcome said drawbacks, which methods avoid the formation of the hydrochloride or any other salt. Examples of said methods can be found in US 5 132 451, US 5 095 148 e US 5 068 413 and they comprise the formation of a cyanic derivative,
10 which is then hydrogenated under drastic conditions to give the free amino acid.

 These methods, however, involve the use of hydrocyanic acid derivatives, which makes them industrially impractical.

15 In a recent patent application, WO-A-98/28255, a novel process for the preparation of the gabapentin starting from the corresponding hydrochloride is described, which allows to solve the problems of the prior art processes, in particular US 4 894 476, connected with the need for
20 evaporating large water volumes at low temperatures to recover free gabapentin.

 Said process comprises the following steps:

- liberation of gabapentin hydrochloride from inorganic salts from the synthesis, by solubilization of
25 gabapentin hydrochloride in organic solvents in which the inorganic salts are insoluble, followed by filtration and evaporation of the solvent;
- displacement of HCl with amines, such as tributylamine, triethylamine and the like, in a solvent in
30 which the hydrochlorides of said amines are soluble but free gabapentin is not soluble, which therefore precipitates in the crystalline form III;
- conversion of gabapentin form III into gabapentin form II.

The present invention aims at providing a process for the preparation of free gabapentin starting from gabapentin hydrochloride, which would overcome the drawbacks mentioned above connected with the process of US 4 894 476, according to alternative procedures to those suggested in WO-A-98/28255.

Said problem is solved, according to the invention, by a process which comprises the steps of:

- preparing a gabapentin hydrochloride aqueous solution;
- adjusting the pH of said solution to or about to gabapentin isoelectric point by addition of a basic compound comprising a monovalent anion;
- diafiltering said solution through a membrane highly selective for organic compounds with molecular weight higher than 150 and poorly selective for inorganic monovalent ions, to separate said solution into an aqueous permeate containing chloride ions and a retentate containing unsalified gabapentin substantially free from chloride ions;
- concentrating said retentate by increasing the pressure exerted on said membrane to obtain a concentration of unsalified gabapentin in the retentate not lower than 5%;
- evaporating the retentate under reduced pressure and at $T^{\circ} < 35^{\circ}$;
- precipitating gabapentin by addition of an alcohol.

The process according to the invention conveniently comprises a further crystallization step of the precipitated unsalified gabapentin with methanol.

The above basic compound is preferably selected from the group consisting of alkali metal and ammonium hydroxides.

The pH of the starting aqueous solution is preferably adjusted to 7.14.

During the diafiltration step, the pressure exerted on the membrane is 10-16 bars, preferably 14-15 bars.

5 During the concentration step, the concentration of unsalified gabapentin in the retentate is preferably brought to an about 8-10% w/v value. During said concentration step, pressure increases gradually to reach a value of about 18-22 bars.

10 During the diafiltration and of concentration steps, temperature is preferably kept below 25°C.

The diafiltration step is preferably carried out with the aid of nanofiltration multilayer composite membranes, such as those sold by PERMEARE S.r.l. (Italy), in particular the membrane named ACN2540HS. Such are membranes have a rejection rate of inorganic salts lower than or equal to 50% and a rejection rate of organic molecules higher than or equal to 96%. Suitable composite membranes have a thin polyamide material coating as the active layer.
15 Other suitable membranes for the process of the invention are those made of polysulfonic resins, nylon, cellulose acetate, polypropylene and polyvinylidene fluoride (PVDF).
20

The process according to the invention solves the problems mentioned above with reference to the prior art processes based on the use of ion exchange resins, by means of a simple technique which requires no drastic operative conditions, such as high temperatures, which would cause the undesired formation of the gabapentin lactam.
25

Further advantages of the process of the invention will be more evident from the following examples.
30

EXAMPLE 1

5 kg of 1-(aminomethyl)-1-cyclohexaneacetic acid.HCl are dissolved in 10 volumes of deionized water at room temperature. This solution is slowly added with about 24 l

of 1 M NaOH to reach pH 7.14 (gabapentin isoelectric point), while cooling to keep the temperature not above 20°C.

5 The resulting solution is subjected to diafiltration, at a temperature of about 22°C, in an about 100 l pilot plant, using a nanofiltration multilayer composite membrane PERMEARE ACN2540HS, having high selectivity for organic compounds with molecular weight higher than 150 (rejection rate higher than or equal to 98%) and low selectivity to
10 inorganic monovalent ions (50% rejection rate).

The pressure exerted on the membrane is about 14 bars and the outlet pressure is about 12 bars.

The permeate is added with deionized water dosing the NaCl in the permeate.

15 Values remain almost steady in the first amounts of permeate, then decrease again. The permeate flow rate is fixed at about 60 l/h. After 4 hours the NaCl in the permeate is 98% on the calculated content. At this point the concentration step is started. Productivity remains
20 high and the pressure increase observed in this step (the inlet pressure is up to about 22 bars and the outlet one to about 20 bars) to keep the permeate flow rate steady is due to an increase in the osmotic pressure following the increase in the solute concentration. When an about 50 l
25 volume is reached, the retentate solution containing about 10% unsalified gabapentin is recovered. Finally the solution is evaporated under reduced pressure and at a temperature < 35°C, reducing the volume from 50 to 10 l, and gabapentin is precipitated by addition of isopropyl
30 alcohol. The precipitated solid is finally recovered by filtration and crystallized from methanol, to obtain 3.3 kg of pure gabapentin.

EXAMPLE 2

5 kg of 1-(aminomethyl)-1-cyclohexanecarboxylic acid HCl

are dissolved in 10 volumes of deionized water at room temperature. This solution is slowly added with about 24 l of 1 M KOH to reach pH 7.14 (gabapentin isoelectric point), while cooling to keep the temperature not above 20°C.

5 The resulting solution is subjected to diafiltration, at a temperature of about 22°C, in the same pilot plant as above, using the membrane PERMEARE ACN2540HS. The pressure exerted on the membrane is about 14 bars and the outlet pressure is about 12 bars.

10 The permeate is added with deionized water dosing the KCl in the permeate.

Values remain almost steady in the first amounts of permeate, then decrease again. The permeate flow rate is fixed at about 55 l/h. After 4 hours, the KCl in the
15 permeate is 98% on the calculated content. At this point the concentration step is started, increasing the inlet pressure to about 22 bars. When an about 50 l volume is reached, the retentate solution containing about 10% unsalified gabapentin is recovered and the same operations
20 as in example 1 are carried out, to obtain 3.25 kg of crystalline unsalified gabapentin.

EXAMPLE 3

5 kg of 1-(aminomethyl)-1-cyclohexaneacetic acid HCl are dissolved in 10 volumes of deionized water at room
25 temperature. This solution is slowly added with about 24 l of 1 M NH₄OH to reach pH 7.14 (gabapentin isoelectric point), while cooling to keep the temperature not above 20°C.

30 The resulting solution is subjected to diafiltration, at a temperature of about 20°C, in the same pilot plant as above, using the membrane PERMEARE ACN2540HS. The pressure exerted on the membrane is about 14 bars and the outlet pressure is about 12 bars.

The permeate is added with deionized water dosing the

NH₄Cl in the permeate.

The flow rate of the permeate is fixed at about 65 l/h. After 4 hours the NH₄Cl in the permeate is 98% on the calculated content. At this point the concentration step is started, increasing the inlet pressure to about 22 bars. When an about 50 l volume is reached, the retentate solution containing 10% unsalified gabapentin is recovered and the same operations as in example 1 are carried out, to obtain 3.3 kg of crystalline unsalified gabapentin.

CLAIMS

1. A process for the preparation of gabapentin starting from gabapentin hydrochloride, which comprises the following steps:

- preparing a gabapentin hydrochloride aqueous solution;

- adjusting the pH of said solution to or about to gabapentin isoelectric point by addition of a basic compound comprising a monovalent anion;

- diafiltering said solution through a membrane highly selective for organic compounds with molecular weight higher than 150 and poorly selective for inorganic monovalent ions, to separate said solution into an aqueous permeate containing chloride ions and a retentate containing unsalified gabapentin substantially free from chloride ions;

- concentrating said retentate by increasing the pressure exerted on said membrane to obtain a concentration of unsalified gabapentin in the retentate not lower than 5%;

- evaporating the retentate under reduced pressure and at $T^{\circ} < 35^{\circ}$;

- precipitating gabapentin by addition of an alcohol.

2. A process as claimed in claim 1, comprising a further crystallization step of the precipitated gabapentin with methanol.

3. A process as claimed in claim 1 or 2, wherein said basic compound is selected from the group consisting of alkali metal and ammonium hydroxides.

4. A process as claimed in claim 3, wherein the pH of said aqueous solution is adjusted to 7.14.

5. A process as claimed in claim 4, wherein the

concentration of unsalified gabapentin in the retentate is brought, during said concentration step, to an about 8-10% w/v value.

5 6. A process according to any one of the above claims, wherein during the diafiltration and concentration steps, the temperature is preferably kept below 25°C.

7. A process according to any one of the above claims, wherein said membrane is a nanofiltration multilayer composite membrane having a rejection rate of organic
10 compounds with molecular weight above 150 higher than or equal to 96%.

8. A process as claimed in claim 7, wherein said membrane comprises a layer made of polyamide, polysulfonic resins, nylon, cellulose acetate or polyvinylidene fluoride.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C227/42 C07C229/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 28255 A (PESACHOVICH MICHAEL ;SINGER CLAUDE (IL); TEVA PHARMA (IL); PILARSK) 2 July 1998 (1998-07-02) cited in the application page 7 -page 12; claims 1-15	1
A	EP 0 340 677 A (WARNER LAMBERT CO) 8 November 1989 (1989-11-08) claims 1-9; examples 1-3 & US 4 894 476 A cited in the application	1
A	US 4 024 175 A (SATZINGER GERHARD ET AL) 17 May 1977 (1977-05-17) cited in the application abstract	1
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

20 June 2000

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl,
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 414 275 A (GOEDECKE AG) 27 February 1991 (1991-02-27) claim 1; examples 5,6 -----</p>	1

INTERNATIONAL SEARCH REPORT

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